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The ageing immune system: can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity?

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Abstract

Remodelling of the immune system with age — immunosenescence — is a significant contributor to poor health in older adults, with increasing risk of infections, cancer and chronic inflammatory disease contributing to age-related multi-morbidity. What is seldom considered when examining the immune response of an aged individual is that the immune system is profoundly influenced by physical activity. Habitual physical activity levels decline with age, with significant consequences for muscle mass and function. Skeletal muscle is a major immune regulatory organ and generates a range of proteins, termed myokines, which have anti-inflammatory and immunoprotective effects. Several studies indicate that maintaining physical activity has immune benefits in older adults; for example, it reduces the systemic inflammation associated with chronic age-related diseases. Herein we discuss how physical activity can prevent or ameliorate age-related multi-morbidity by boosting immune function and consider whether physical activity could improve immunotherapy outcomes in age-related conditions such as cancer.

[H1] Introduction

There is a continuing trend for increased human life expectancy across the globe, particularly in the developed countries[1]. Between 1990 and 2010, life expectancy in the UK increased by 4.2 years in men and 1.9 years in women, but healthy life expectancy **[G]** did not keep pace, increasing at approximately half this rate[2]. We are thus living longer, but not healthier. Furthermore, ill health in old age is typically not due to any one disease, but instead many older adults are multi-morbid – defined here as the presence of two or more chronic conditions. For example, in a retrospective study of disease incidence in Minnesota from 2005-2010, 22% of adult patients overall had two or more conditions and this rose to 77% in the over 65 year old group[3]. Understanding the drivers of age-related multi-morbidity and developing interventions to prevent or delay its occurrence is now a priority in many countries.

It is often not appreciated that increased population longevity is a relatively recent phenomenon, beginning around 250 years ago[4]. This is a relatively short time in the context of our genetic heritage, where our global physiology and accompanying immune system evolved to meet the demands of an active hunter–gatherer lifestyle[5] (**Figure 1**). Our modern lifestyle goes against the blueprint laid down by this genetic inheritance, with inactivity and overeating resulting in impaired function across a range of systems in old age[6], culminating in multi-morbidity and increased incidence of cardiovascular disease, obesity, type 2 diabetes and cancer[6]. Thus it is becoming increasingly clear that being sufficiently physically active across the life course is a central requirement for achieving a healthy old age[7]. Moderate to vigorous physical activity and cardio-respiratory fitness are both key predictors for reduced all-course mortality[8,9], and the reverse is true for sedentary behaviour such as sitting or lying down[10,11]. Indeed, large cohort studies have revealed that physical activity and time spent being sedentary are independent variables affecting health and the ideal is to maintain adequate levels of physical activity and minimise sedentary time[11]. Unfortunately, physical activity tends to decline dramatically with age. For instance, less than 10% of UK adults aged over 65 meet the Chief Medical Officer's recommendation for physical activity of 150 minutes of aerobic exercise a week. Further, as the immune system is readily influenced by physical activity[12], increased inactivity across the lifespan may also contribute to reduced immunity in old age.

In this Review, we discuss the evidence suggesting that reduced physical activity with age is a major contributor to age-related immune decline, which in turn pre-disposes the individual to multi-morbidity. Physical activity and exercise are often used interchangeably (see Box 1). Here, physical activity is used to refer to the sum of any general body movement that raises energy expenditure above a basal level, whereas exercise denotes a specific form of physical activity, such as cycling or swimming, carried out for a set purpose. We consider active skeletal muscle as a major immune regulatory organ, with inactivity and sarcopenia **[G]** providing a mechanistic link between low levels of physical activity, age-related immune decline and the chronic diseases of old age. The potential of physical activity as an immune adjuvant to enhance responses to vaccines and immune-based cell therapies in older adults is also discussed.

[H1] Physical activity and immune health

An optimally functioning immune system is central to health, with cellular and humoral immunity required for protection against infections, responses to vaccines, detection and removal of cancers, and prevention of autoimmune disease. The immune system does not operate in isolation and is profoundly influenced by environmental factors, including physical activity[12]. Consequently, an association between physical activity, immunity and disease has been demonstrated in a range of population-level studies. Participation in regular bouts of moderately intense physical activity (for example, brisk walking or swimming), of at least 150 minutes per week, confers protection against a myriad of immune and inflammatory disorders, as well as multi-morbidity and mortality[13-15]. Prospective studies have consistently shown that regular physical activity reduces the risk of infection[16,17] and the burden of latent viral infections[18]. There is also ample evidence that physically active lifestyles reduce the risk of cancer, particularly those that disproportionately afflict older individuals, such as breast, colon and prostate cancer[19]. The benefits of physical activity are also apparent in older adults in the context of protection against frailty and cognitive impairment[20,21]. We therefore suggest that many of the benefits of physical activity on health are achieved through positive effects on the immune system.

An emerging body of work in animal models and humans also supports causative links between increased physical activity and disease prevention and management mediated by improved immunity. Rodent models have shown that moderate exercise can improve survival in mice infected with a lethal dose of influenza virus[22]. Here, protection was attributed to a reduction in inflammatory cell infiltration and a shift from a T helper 1 (Th1)- to a Th2-type cytokine profile in the lung[23]. Influenza and pneumonia remain major causes of death amongst older adults and prophylactic vaccination is less effective in this population, especially in those who are frail[24]. Exercise interventions have been shown to improve immune responses to both novel and recall antigens in seniors[25], with two clinical trials in aged humans showing that increased physical activity can improve immune responses and extend protection provided by the influenza vaccine[26,27]. Exercise interventions have also been shown to improve disease symptoms in a range of inflammatory and autoimmune disorders, with the benefits seen including improvements in micro- and macrovascular function[28] and decreased disease severity and pain in patients with rheumatoid arthritis[29]. Consequently, there is increasing interest in whether physical activity can preserve immunity into old age and thereby protect against multi-morbidity.

[H1] Ageing and immunity

The decline in immunity with advanced age has been termed *'*immunosenescence' and contributes significantly to ill health in old age. For example, immunosenescence is associated with reduced efficacy of vaccinations[30], increased susceptibility to viral and bacterial infections[31], re-emergence of latent viruses (such as varicella zoster virus, which causes shingles[32]) and reduced immune surveillance potentially contributing to increased cancer incidence[33]. Another aspect of ageing that is, in part, influenced by immunosenescence is the increase in systemic inflammation, so-called 'inflammageing'. Inflammageing is likely a generic driver of age-related multi-morbidity as the degree of inflammageing has been related to increased risk of most chronic diseases of old age[34,35]. Indeed, the influence of an active lifestyle on health in old age may lie in its impact upon inflammageing, as regular physical activity has been associated with reduced systemic inflammation in older adults[36,37].

[H2] Key features of the immune system in older adults.

Advanced age is associated with remodelling of both the innate and adaptive arms of the immune system which can eventually lead to compromised immunity and disease. As there have been many comprehensive and recent reviews of the changes to the innate and adaptive immune systems with age, we have summarised the key features of immunosenescence in **Table 1**. Key elements include: compromised migration and anti-microbial function in neutrophils and monocytes, reduced natural killer (NK) cell cytotoxicity, reduced quality and quantity of antibody production by B cells, thymic atrophy and increased frequency of highly differentiated T cells that are often considered to be senescent due to their reduced proliferative capacity. Interestingly, these highly differentiated memory T cells[38], as well as memory B cells[39], exhibit secretion of pro-inflammatory cytokines similar to the senescence associated secretory phenotype (SASP) **[G]** seen in non-immune senescent cells, thereby contributing to inflammageing **[G]**.

Crucially, studies in both mice[40] and humans[41] have identified a suite of immune parameters as markers of biological age, suggesting that immunosenescence is an integral component of the ageing process and a driver rather than a consequence of age-related disease. In support of this proposal, several features of T cell immunosenescence are seen in the early stages of rheumatoid arthritis with no association with the duration of symptoms[42], suggesting that immune ageing precedes rheumatoid arthritis rather than being a consequence of disease. Furthermore, other chronic inflammatory diseases that occur in childhood, such as spondyloarthropathies, do not show accelerated immunosenescence[43].

[H2] Lifelong physical activity and amelioration of immune ageing.

The contribution of the age-related decline in physical activity to immunosenescence has received little attention but is likely to be a significant confounder in studies of immunity in older adults. The effects of maintaining physical activity throughout adulthood on immune ageing also remain largely unexplored as most studies of the 'long term' effects of increased physical activity have only lasted for 6-12 months. To address this issue, one study assessed immune cell phenotypes in physically active male and female non-elite cyclists (n=125) who had maintained a high level of physical activity for much of their adult lives. These older

adults, aged 55-79 years, showed few of the changes in physiological function routinely reported with advancing age, such as loss of muscle mass and function (sarcopenia), reduced insulin sensitivity, elevated cholesterol and high blood pressure[44]. The cyclists also showed few signs of immunosenescence, including reduced evidence of a decline in thymic output, with a frequency of recent thymic emigrants similar to that seen in young adults[45]. Systemic inflammation and induction of Th17 cell responses were also not increased and changes to regulatory T and regulatory B cell frequencies previously reported in aged humans[46,47] were not seen in the cyclists. However, accumulation of $CD28^{-}CD57^{+}$ T cells with a senescent/exhausted phenotype still occurred and the frequency of these cells did not differ from age-matched non-exercising adults, suggesting that lifelong physical activity ameliorates rather than totally prevents immunosenescence[45].

In a second study of healthy males aged 18-61 years (n=102) a positive correlation between aerobic fitness (VO_2max **[G]**) and the frequency of naive T cells was also reported, though this study also found reduced levels of senescent $CD28^{-}CD57^{+}$ $CD4^{+}$ and $CD8^{+}$ T cells in the adults in the highest tertile for VO_2max[48]. Improvements in thymic output might be due to effects of physical activity on the senescent/exhausted T cell pool. Physical activity has been shown to increase apoptosis of T cells with a senescent/exhausted phenotype[49], which might increase the generation of progenitor cells[50] to maintain a richer pool of naive cells with advancing age.

The benefit of maintained thymic output and naive T cell frequency in habitual exercisers was also suggested by a study of 65-85 year old men who had undertaken a moderate or high intensity level of physical activity for an average of 25 years. These adults showed higher antibody responses to influenza vaccination than age-matched controls who were not regular exercisers[51].

Taken together, these studies suggest that the emergence of certain features of immunosenescence and the extent of immune remodelling is likely to be heavily influenced by insufficient physical activity as humans age.

[H1] Mechanism of immune protective effect

[H2] Skeletal muscle as an immune regulatory tissue.

Skeletal muscle is now recognised as an endocrine organ, capable of expressing and secreting cytokines (referred to as myokines) into the circulation during physical activity (**Figure 2**). IL-6 was the first myokine identified. It is produced soon after the onset of physical activity, with the levels produced depending on the intensity and duration of activity[52], reflecting muscle mass and contractile activity. IL-6 is a pro-inflammatory cytokine when it is generated via the NF-κB signalling pathway in response to cytokines such as TNF that are produced during infection or after tissue damage. In contrast, IL-6 generated in response to exercise is anti-inflammatory, is induced via JUN N-terminal kinase (JNK) and activator protein 1 (AP1) signalling[53] and leads to the production of regulatory mediators (such as IL-10 and IL-1 receptor antagonist (IL-1RA)) by monocytes and macrophages[54]. IL-6 also stimulates the release of cortisol from the adrenal glands, thereby providing a second anti-inflammatory signal[55]. The benefit of IL-6 produced from exercising muscle was indicated in young adults in an experimental model of 'low-grade inflammation' in which the increase in plasma TNF concentration induced by low-dose administration of *E. coli* endotoxin was entirely blunted by 3h of prior ergometer cycling. These effects of physical activity were also mimicked by an infusion of IL-6, which similarly suppressed the endotoxin-induced TNF production[56]. Other novel myokines released from exercising muscle have also been reported to have metabolic and immune effects. Meteorin-like is a myokine that can induce 'browning' of adipose tissue, stimulate an eosinophil-dependent increase in IL-4 and promote the polarisation of M2-like macrophages **[G]**[57]. Whilst there are no data concerning net release of IL-6 or other myokines from skeletal muscle during physical activity in older people, increasing physical activity and reducing sedentary behaviour in older adults has been associated with lower levels of pro-inflammatory cytokines[58].

In addition to IL-6, other cytokines such as IL-7[59] and IL-15[60] are expressed and released by exercising muscle. IL-7 is required for thymocyte development[61], IL-7 and IL-15 are lymphocyte proliferative factors (especially for naive T cells[62]) and the serum levels of these cytokines declines with age[45]. The potential mechanisms by which regular physical activity exerts a positive effect on thymic output and naive T cell numbers is likely to involve these myokines. In the study of older cyclists described above, these adults had higher serum levels of IL-7 and IL-15 compared with non-exercising older adults[45]. IL-15 also has metabolic effects protecting against visceral adiposity by preventing lipid deposition in pre-adipocytes

and reducing white adipose tissue[63]. As fat accumulation in the thymus is a hallmark of thymic cellular atrophy in humans[64], increased IL-15 may also protect the thymus during ageing. However, a recent study comparing IL-15 expression by adipose tissue and skeletal muscle in older adults reported that adipose tissue had higher expression of IL-15 and that serum IL-15 levels correlated with visceral fat mass but not muscle mass[65]. IL-15 is also required for NK cell development and cytotoxicity and the authors suggested that fat-derived IL-15 may support NK cell-mediated immunity in older adults. However, no details of the physical activity levels in these participants were provided. In lean older adults involved in regular physical activity we would argue that muscle is a major source of IL-15. Importantly, muscle is not associated with the adverse effects of adipose tissue, which is pro-inflammatory in nature and secretes a range of cytokines and adipokines that can contribute to inflammageing (Box 2).

Overall, the myokine hypothesis provides a framework that connects active skeletal muscle to the maintenance of a healthy immune system during ageing as physical inactivity, with age-related sarcopenia, both limit the immune regulatory function of muscle in old age. In addition, with the rapid progress of omics technologies, other proteins, RNA, or miRNA released from active skeletal muscle, possibly encased in exosomes, might well provide a greater understanding of this interaction with the immune system. Indeed a recent study revealed that 1 hour of cycling liberated high levels of extracellular vesicles, containing potentially novel myokines that were released into the circulation via this classical secretion independent route[66].

[H2] Effects of physical activity on innate immune cell function.

Cross-sectional studies comparing sedentary and low-fitness elders with their physically active, highly fit peers have demonstrated multiple benefits for the innate immune system in addition to the T cell population changes described above (**Figure 3**). Regular physical activity in old age is associated with enhanced NK cell function[67] and the maintenance of neutrophil bactericidal function and migratory dynamics[68]. In addition, exercise interventions have been shown to lower the numbers of circulating $CD16^{+}$ inflammatory monocytes[69], and improve neutrophil oxidative burst and phagocytosis[70]. Physical activity can also lower fat mass, reducing infiltration of inflammatory monocytes to adipose tissue and increasing polarisation

of adipose tissue-resident macrophages from an M1-like pro-inflammatory to an M2-like anti-inflammatory phenotype[71]. This mechanism has been proposed to prevent or reverse chronic low-grade inflammation in adipose tissue that could otherwise contribute to the development of inflammageing with increased risk of age-related disease and multi-morbidity.

Physical activity and control of latent viral infection.

One other mechanism by which involvement in regular physical activity might contribute to prevention of immunosenescence, specifically age-related T cell remodelling, is through improvements in viral control. Accelerated T cell differentiation and exhaustion is partly driven by cytomegalovirus (CMV) infection, a prevalent latent herpes virus that persists for the lifetime of the host[72]. The virus is capable of periodic and subclinical reactivation, placing a significant burden on the T cell compartment. Moreover, CMV seropositivity has been linked with frailty, cognitive decline and poor immune responses to vaccines in older adults[73]. A recent cross-sectional study in a large (n=~1400) ethnically diverse cohort aged 21-91 years revealed inverse relationships between cardiorespiratory fitness and latent viral control, with the impact of VO_2max on CMV control being more marked in those aged >65yrs[18]. These findings indicate that high cardiorespiratory fitness levels may protect against latent viral reactivation, which in turn will delay immunosenescence. Although the mechanisms through which physical activity can improve latent viral control remain to be determined, it is possible that each bout of physical activity causes an augmented redistribution of catecholamine-sensitive $CD8^+$ T cells with viral antigen specificity and a highly differentiated phenotype and that this increases anti-viral immune surveillance and helps to lower viral loads[74,75]. However, CMV serostatus is not always assessed in studies of physical activity and immunity and we would advocate that this must be done as it is another potential confounder in such analyses.

[H2] Catecholamines and lymphocyte β2 adrenergic receptor signaling.

Single bouts of exercise elicit a rapid and preferential mobilisation of lymphocyte subtypes with phenotypes associated with enhanced effector function, tissue migration, catecholamine sensitivity and antigen specificity[76]. NK cells are the most responsive group of lymphocytes, with even very brief physical activity causing 4-5-fold increases in peripheral

blood NK cell numbers[77]. These effects of physical activity are mediated through the β2-adrenergic receptor (β-AR) subtype[78]. The mobilisation of cytotoxic lymphocyte subtypes by catecholamines following exercise provides a possible mechanism for why frequent bouts of acute dynamic physical activity can protect against cancer. Pedersen *et al.* reported that voluntary wheel running reduced tumour incidence and growth by approximately 60% across five different mouse tumour models[79]. Depleting NK cells and repeating the experiments in athymic mice, which lack T cells but retain functional NK cells, confirmed that the anti-tumour effects of exercise were NK cell-mediated in mice. T cells mobilised by physical activity are more responsive to *ex vivo* stimulation with tumour antigens such as WT-1, PRAME and MAGE-A4[80]. More recent work has shown that catecholamines present in plasma taken following a single exercise bout in healthy controls and in patients with breast cancer can reduce the viability of hormone-sensitive and hormone-insensitive breast cancer cell lines in vitro and mitigate tumour growth in vivo when the plasma-treated cells are transplanted into immune-compromised mice[81]. Taken together, these findings indicate that catecholamines released during physical activity play an important role in priming the tumour microenvironment as well as in facilitating the mobilisation and redistribution of tumour-infiltrating lymphocytes, especially myokine-sensitive NK cells.

[H2] CMV and age-related declines in NK cell β-AR sensitivity.

Ageing is the biggest risk factor for acquiring cancer and it is known that older adults mobilise fewer T cells and NK cells in response to intensity-controlled physical activity compared to their younger counterparts[82]. Furthermore, although the density of β-AR expression on lymphocytes is unaltered with ageing, β-AR sensitivity is substantially reduced[83]. Interestingly, previous exposure to CMV markedly inhibits NK cell mobilisation in response to exercise due, in part, to a CMV-induced increase in the proportion of NK cells expressing the activating receptor NKG2C, which respond poorly to catecholamines[84]. This suggests that CMV infection, and not age *per se*, is responsible for reducing the mobilisation and redistribution potential of the NK cell compartment in response to physical activity. Given that the catecholamine-dependent redistribution of NK cells appears to be a fundamental mechanism by which physical activity can inhibit cancer acquisition and progression[79], it is possible that those with

CMV might not get the same anti-tumour surveillance benefits of regular physical activity as their non-infected counterparts. Future studies investigating the effects of physical activity on NK cell catecholamine sensitivity and redistribution in the context of CMV and anti-cancer immunity are warranted.

[H2] Physical activity and gut microbiota diversity.

The intestinal microbiota plays an important role in the maintenance of host health and immunological protection. It is relatively stable throughout adult life until there is a marked reduction in biodiversity in old age[85]. This altered microbiota profile includes an increase in facultative anaerobes, including *Streptococci* and *Enterobacteria* and a decline in bacteria considered to be health promoting, such as *Bifidiobacterium* and *Lactobacillus*[86,87]. Furthermore, age-related impairment in innate immune defences (such as anti-microbial peptides, reactive oxygen species and α-defensins) favours bacterial overgrowth on epithelial surfaces and enterocytes respond by forcing an inflammatory response that drives dendritic cell-mediated differentiation of Th1 and Th17 cells[88].

A role for reduced gut microbiota diversity in immunosenescence is only now being considered, though data supporting a causative link are restricted to rodent studies. In older humans[89] and mice[90] there is an association between microbiota diversity and systemic inflammation. Theveranjan *et al.* have reported that aged germ-free (GF) mice did not display inflammageing, their macrophage bactericidal function was intact and they did not have the raised leukocyte infiltration in the lungs seen in old non-GF mice. The GF mice were also longer-lived than control littermates[91]. To confirm that reduced microbial diversity was responsible for the raised systemic inflammation, rather than the presence of any microbiota, two approaches were used: the study generated mice with a minimal microbiota of low microbiota diversity and still saw an increase in serum IL-6 with age. Co-housing GF mice with old but not young traditionally housed mice also raised their systemic inflammation[91].

The earliest evidence for beneficial effects of physical activity on the gut microbiota came from Matsumoto and colleagues, who reported an increase in gut microbiota diversity in exercised rats[92]. There is currently a paucity of human interventional studies examining the effects of physical activity on gut microbiota, particularly in older adults. One observational

study in elite rugby players has reported an increased relative abundance of *Firmicutes* with a reduced abundance of *Bacteroides*[93]. Allen *et al.* showed differential alterations in gut microbiota composition in lean and obese humans following a six week exercise intervention programme; specifically, they found an increased abundance of *Faecalibacterium* and *Lachnospira* with a reduced abundance of *Bacteroides* in lean participants, whereas an increased abundance of *Bacteroides* was seen in the obese participants. These changes reversed when the participants returned to their sedentary lifestyles[94]. However, the relationship between physical activity, gut microbiota and mucosal immunity across the life-course remains under researched.

[H1] Physical activity as a therapy

[H2] Physical activity as an immune adjuvant.

The strongest evidence to date supporting physical activity as a powerful immune adjuvant comes from vaccination studies in older adults. Periods of extended physical activity involvement, maintained high levels of habitual physical activity in old age and single bouts of exercise prior to vaccination have all been shown to improve immune responses to the influenza and pneumococcal vaccines[26,27,51] as well as to experimental vaccines that contain novel antigens, such as keyhole limpet haemocyanin (KLH)[25]. The mechanism of action is likely a composite of localised inflammation and an infiltration of phagocytic and antigen-presenting cells at the site of inoculation, priming of the T cell response, increased naive T cell frequency and improvements in B cell function[25,45,48]. Both dynamic whole-body exercise and localised resistance exercise that cause transient damage to the deltoid muscle prior to inoculation increase immune responses to the vaccine. However, more acute low-intensity exercise interventions, such as a single bout of 45 minutes brisk walking[95], or 40-minute treadmill walking at an intensity of 55%-65% of maximum heart rate[96] prior to vaccination, have so far failed to show any major or consistent improvements in vaccine responses in older adults.

As already stated, ageing remains the most significant risk factor for cancer development and there are many instances when cancer immunotherapy is less effective in the old[97]; this is particularly true for responsiveness to PD1, PDL1 and CTLA4 immune

checkpoint blockade therapy, chemotherapy and tyrosine kinase inhibitors. The degree to which changes in immune phenotype and function with age contribute to cancer development is unknown, though loss of cytotoxic function of NK cells and $CD8^+$ cytotoxic T cells for example would likely reduce immune surveillance capabilities in older people. In an era of precision medicine, genetic engineering and immunotherapy, simple increases in physical activity may prove to be an effective adjuvant to both limit toxicity and increase the efficacy of cancer treatments, even against the backdrop of an aged immune system (reviewed in Ref. 98). However, a challenge facing patients with cancer is that they are often too sick and frail to undertake the required level of physical activity due to the debilitating nature of their cancer treatment. To circumvent this, physical activity interventions are now being delivered before initiating treatment in a procedure referred to as 'pre-habilitation'[99]. A programme that comprised both aerobic and resistance exercise lasting approximately 24 days prior to surgery for colorectal cancer significantly improved post-surgery recovery of physical function[100]. That pre-habilitation may be effective is further suggested by the observation that higher aerobic fitness (VO_2max) levels prior to haematopoietic stem cell transplantation are inversely associated with risk of mortality and time spent in hospital[101].

Physical activity might also help facilitate the recovery and manufacture of immune cells for immunotherapy. Single bouts of exercise increase the recovery and *ex vivo* manufacture of virus-specific T cells from virus-experienced healthy donors for the prophylactic and therapeutic treatment of post-transplant viral infections[74,75]. Exercise has also been shown to augment the *ex vivo* manufacture of tumour-antigen-specific T cells from healthy donors in preparation for allogeneic adoptive transfer immunotherapy as a means to prevent and treat relapse after allogeneic stem cell transplantation[80]. Moreover, single bouts of exercise mobilise CD34+ hematopoietic stem cells in to the bloodstream via the β2-AR and may serve as an adjuvant to recover more progenitor cells from the peripheral blood of healthy granulocyte colony-stimulating factor (G-CSF) mobilized donors prior to transplantation[102].

[H2] Physical activity as a therapy to prevent age-related multi-morbidity.

Advanced age is the single largest risk factor for multi-morbidity[2] and there is now increased evidence from animal models that interfering with core ageing processes extends lifespan but also prevents a broad range of age-related diseases[103]. Whilst the current focus of this research is on pharmacological interventions to inhibit ageing processes[104], it is worth considering that the broad health benefits of physical activity may be mediated through an impact upon basic ageing mechanisms. Until recently, the rate of an individual's biological ageing was difficult to determine but in 2013 Horvath published an algorithm, the epigenetic clock, based on leukocyte DNA methylation at 350 CpG sites that correlated closely with chronological age and deviations from this association were indicative of increased mortality and morbidity[105]. A few studies are now emerging that have determined associations between physical activity and this biomarker of biological age. One study of over 4500 adults revealed that physical activity had a beneficial effect on the rate of epigenetic ageing as determined by this biomarker[106]. A smaller cross-sectional study of 248 seventy-nine year olds found no association between the epigenetic biomarker and physical activity levels measured objectively by accelerometry over 7 days[107], though life-long involvement in physical activity may be the more important determinant of biological ageing[6]. An analysis of the same cohort from age 70 to 76 did reveal an association between an individual's physical fitness (lung function, hand grip strength), with poorer function linked to a higher rate of change in DNA methylation[108].

Although ageing is a highly complex process, through research in model organisms we are now beginning to understand many of the biological mechanisms driving ageing **[G]**[109]. These include reduced DNA damage repair, telomere shortening, reduced autophagy and compromised proteostasis, all potentially leading to induction of cell senescence. Several observational studies have shown an association between physical activity levels and telomere length, for example an analysis of data from 7813 women in the Nurse's Health Study showed a modest positive benefit of physical activity on leukocyte telomere length[110]. A 30 year longitudinal study has shown that adults who undertook moderate levels of physical activity had longer telomeres in old age than those who did either low or very high levels of activity[111], suggesting a dose-dependent effect on telomere length. Fewer researchers have carried out interventional studies to determine causality. A small 5 year study in men (n=10) with low risk prostate cancer were prescribed increased physical activity and showed longer

telomere length and higher telomerase activity compared with 25 controls with clinical surveillance only[112]. In contrast, a 12 month randomised controlled study of aerobic exercise in 200 post-menopausal women found no evidence of an improvement in the rate of leukocyte telomere shortening[113]. It is possible that 12 months of increased physical activity is not sufficient to modulate telomere shortening.

Senescent cells are proliferatively quiescent but metabolically highly active and contribute to ageing in several ways, including through their secretion of pro-inflammatory cytokines (the so-called senescence-associated secretory phenotype (SASP)) thus supporting the development of inflammageing. Removal of senescent cells has been shown to prevent age-related disease and extend lifespan in mice[103]. One tissue where senescent cells accumulate is adipose tissue and Schafer *et al.* have shown recently that exercise can prevent accumulation of these cells in diet-induced obesity in mice[114]. Physical activity is also able to increase autophagy, including in muscle[115], which will have benefits for metabolism and proteostasis.

Physical activity may thus be able to counteract mechanisms associated with ageing including modulating telomere shortening, cell senescence, autophagy, inflammation and epigenetic changes and thereby ameliorate the ageing phenotype including the multi-morbidity of old age. As immune cells from older adults also demonstrate the presence of these ageing mechanisms, including telomere shortening[116], reduced autophagy[117], a pro-inflammatory phenotype[38,39] and epigenetic changes associated with biological age[105], physical activity may also mediate its beneficial effects on immunity by counteracting these core processes.

[H1] Conclusions

Hippocrates in 400 BC claimed that “Walking is man’s best medicine” and it is clear that physical activity has broad impacts upon health across the life course, many mediated through improved immunity and reduced systemic inflammation[12]. Maintaining a high level of physical activity across the lifespan is arguably the blueprint passed down from our evolutionary heritage and can ameliorate most of the typical aged phenotype, including immunosenescence[44,45,98]. To firm up the case for a causative link between physical activity,

immunosenescence and health much more interventional studies in humans are required. The link between immunosenescence and disease also requires further evidence to show reduced morbidity when immune ageing is selectively targeted. To date this has only been achieved following short-term treatment with rapamycin analogues to inhibit mammalian target of rapamycin (mTOR), which was shown to improve responses to influenza vaccines in older adults and reduce influenza-like infections[118]. If physical activity interventions can then be shown to modulate the immune system through the same mechanisms (for example, through inhibition of mTOR), this will help to provide support for the direct benefits of physical activity for ameliorating immunosenescence. Furthermore, the current literature reports that physical activity is useful as an adjuvant to immunotherapies such as vaccination and immune cell therapy. It is important going forward to stratify physical activity prescription for dose and intensity and to determine in which age-related diseases it will be effective.

Box 1: Definitions of physical activity and exercise

The US Centers for Disease Control and Prevention defines physical activity as "Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level. Physical activity generally refers to the subset of physical activity that enhances health." Exercise is defined as "A subcategory of physical activity that is planned, structured, repetitive, and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective."

Box 2: Adipose tissue and inflammageing

Adipose tissue produces a range of pro-inflammatory cytokines, termed adipokines. In addition, adipose tissue contains macrophages and senescent cells that contribute to the pro-inflammatory output. The increase in adiposity with age thus contributes to inflammageing and in turn to age-related disease.

Figure 1. The evolution of increased longevity

Our nearest primate relatives such as chimpanzees and gorillas live for approximately 10-15 years in the wild once they reach maturity. 5 million years of evolution resulted in a doubling of life expectancy in the hunter-gatherer tribes such as the Ache and Hiwi and this lifespan persisted into the modern 18th century humans. Just 250 years later, as a result of improved sanitation and health care, life expectancy has doubled again[4] and our modern more sedentary lifestyle is thus maladjusted to our genetic inheritance with consequences for health in old age.

Figure 2. Muscle as an immune regulatory organ

In the absence of infection skeletal muscle is a major source of cytokines, termed myokines. Active muscle produces a range of myokines including IL-6 which has anti-inflammatory actions via the induction of IL-10 and IL-1RA by monocyte/macrophages. Muscle derived IL-15 has a range of actions including promoting the survival on naïve T cells, enhancing NK cell production and cytotoxicity and influencing fat deposition by inhibition on lipogenesis. IL-7 has thymoprotective actions helping to maintain thymic output. Skeletal muscle also produces a range of growth factors, including IGF-1 and Meteorin-like (MTRNL) which promote conversion of white to brown adipose tissue, increases IL-4 secretion and

macrophage M2 polarisation. Increased physical activity leads to reduced intermuscular adipose tissue, which is a source of the inhibitory muscle growth factor myostatin.

Figure 3. Physical activity as an immune adjuvant

Maintaining a physically active lifestyle prevents age-related declines in lymphocyte β_2-adrenergic receptor (β_2-AR) sensitivity, allowing for the catecholamine-mediated redistribution of NK cells and viral-specific T cells (VSTs) between the blood and tissues with each bout of physical activity. Lymphocytes and monocytes mobilised in to the blood with physical activity can potentially be collected for immune cell therapeutics (e.g. allogeneic adoptive transfer immunotherapy). The frequent redistribution of NK cells and VSTs with each exercise bout increases immune surveillance, reducing the frequency of latent viral reactivation. This in turn reduces the antigenic load placed on the T cell compartment and prevents the accumulation of senescent/exhausted T cells whilst also maintaining the number and diversity of peripheral naïve T cells. Physical activity can also increase apoptosis of senescent/exhausted T cells which increases the production of hematopoietic progenitor cells. Maintaining a diverse pool of naïve T-cells with physical activity with advancing age will reduce infection risk and increase protection provided from vaccines.

Table 1. Changes to immune cell numbers, phenotype and function with age.

Cell type or tissue	Effects of ageing on cell numbers and phenotype	Effects of ageing on cell functions	References
Neutrophil	Increased numbers	Decreased chemotactic accuracy; decreased bactericidal properties (e.g. phagocytosis , ROS and NET generation)	119,120
Monocyte	Increased total numbers; increased proportions of $CD14^{+}$ 16^{++} non-classical monocytes; decreased proportions of $CD14^{+}$ 16^{-} classical monocytes; equivalent levels of TLR2, TLR4, TLR5 expression	Decreased phagocytosis, efferocytosis, ROS generation; increased basal production of pro- inflammatory cytokines; decreased cytokine production in response to LPS, TLR1/TLR2 or TLR7 stimulation; equivalent cytokine production following TLR2/TLR6, TLR4, and TLR5 stimulation	121,122
NK cell and NKT cells	Increased total NK cell and NKT cell numbers; decreased invariant NKT cell numbers; increased proportions of $CD56^{Dim}$ NK cells; decreased expression of CD94, KLRG1, NKp46 expression on NK cells	Reduced NK cell-mediated cytotoxicity at the single-cell level; reduced perforin release; equivalent levels of NK cell-mediated antibody-dependent cell cytotoxicity	123,124
Dendritic cell	Decreased or equivalent numbers of plasmacytoid DCs and myeloid DCs;	Reduced phagocytosis; reduced recruitment to lymphoid organs; reduced induction of T	125,126

	Equivalent levels of MHC II, CD11c and CD123 expression; equivalent levels of TLR7 and TLR9 expression	cell proliferation , IFNγ and IL-12 secretion	
Thymus	Decreased stromal cell and thymocyte cellularity; decreased numbers of double-positive thymocytes; increased adipocyte infiltration; decreased levels of thymus-enhancing cytokines (e.g. IL-7 and KGF); increased levels of thymus-suppressive cytokines (e.g IL6 and TNF)	Decreased naïve T cell output; decreased numbers of recent thymic emigrants	127,128
T cell	Decreased CD3+ T cell numbers; decreased proportions of naive T cells, increased proportions of memory T cells; increased proportions of T cells with senescent/exhausted phenotype ($CD28^{-ve}$, $CD57^{+ve}$,$KLRG1^{+ve}$, $PD1^{+ve}$); increased proportions of regulatory T cells	Decreased T cell proliferation; increased secretion of pro-inflammatory cytokines; decreased CD4+ helper T cell activity; decreased CD8+ T cell cytotoxicity; increased Th17 cell polarisation	38, 46, 129, 130
Bone marrow	Decreased numbers of pre-B cells; fewer niches for B cell development	Reduced expression of transcription factors crucial for B cell differentiation (e.g. E47); reduced secretion of IL-17 by stromal cells; decreased B cell lymphopoiesis	131,132
B cell	Decreased total B cell numbers; decreased proportions of naive B cells and regulatory B cells, increased	Reduced antibody production, clonal diversity and lower antibody affinity; lower IL-10 secretion by regulatory B cells	39,47

	proportions of memory B cells		

Abbreviations: ROS, Reactive oxygen species; NET, neutrophil extracellular trap; TLR, Toll-like receptor; LPS, lipopolysaccharide; TNF, tumour-necrosis factor; KLRG1, killer cell lectin-like receptor subfamily G member 1; NKp46, natural killer cell p46-related protein; KGF, keratinocyte growth factor;

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Competing interests

The authors declare no competing interests.

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Glossary terms

Healthy life expectancy.
Life expectancy is the predicted total number of years an individual is likely to live and the proportion of life that will be spent in good health is termed healthy life expectancy or healthspan.

Sarcopenia.
Sarcopenia refers to a condition of low muscle mass and function (strength) and commonly occurs with age or chronic illness. The European Working Group on Sarcopenia in Older People has defined low muscle mass as >2 standard deviations from the mean value for young adults and low strength as a walking speed of less than 0.8m/s and hand grip strength of <30 kg in males, <20 kg in females.

M1 and M2-like macrophages.
'M1' and 'M2' are classifications historically used to define macrophages activated *in vitro* as pro-inflammatory (when 'classically' activated with IFN and LPS) or anti-inflammatory (when 'alternatively' activated with IL-4 or IL-10), respectively. However, *in vivo* macrophages are highly specialized, transcriptomically dynamic and extremely heterogeneous with regards to their phenotypes and functions, which are continuously shaped by their tissue microenvironment. Therefore, the M1 or M2 classification is too simplistic to explain the true nature of *in vivo* macrophages, although these terms are still often used to indicate whether the macrophages in question are more pro- or anti-inflammatory.

Biological mechanisms driving ageing.
The biological mechanisms driving the ageing process in many species have been proposed to consist of various responses to cell and organelle damage. They include the accumulation of senescent cells, altered nutrient sensing, reduced mitochondrial fitness and stem cell function. Inflammation is one of the key downstream mediators as senescent cells release pro-inflammatory cytokines.

Senescence-associated secretory phenotype (SASP).
Senescent cells are classically proliferatively quiescent but highly active metabolically. They have a rich secretory output termed the SASP, which contains pro-inflammatory cytokines and chemokines, matrix metalloproteinases and growth factors such as VEGF. The SASP is thought to be a key mediator of the ageing process.

Inflammageing.
Inflammageing describes the two to four fold increase in systemic levels of inflammatory cytokines (e.g. TNF, IL-1β and IL-6) and reduced levels of anti-inflammatory cytokines (e.g. IL-10) seen with advanced age. The degree of inflammageing is associated with increased risk of a range of age-related diseases including cardiovascular disease, osteoporosis, cancer and dementia.

VO_2max.
VO_2 max is the maximum rate of oxygen consumption measured during incremental exercise. The value is a measure of an individual's cardiorespiratory fitness as it represents the maximum rate at which the heart, lungs and muscles can use oxygen during exercise.

Figure 1

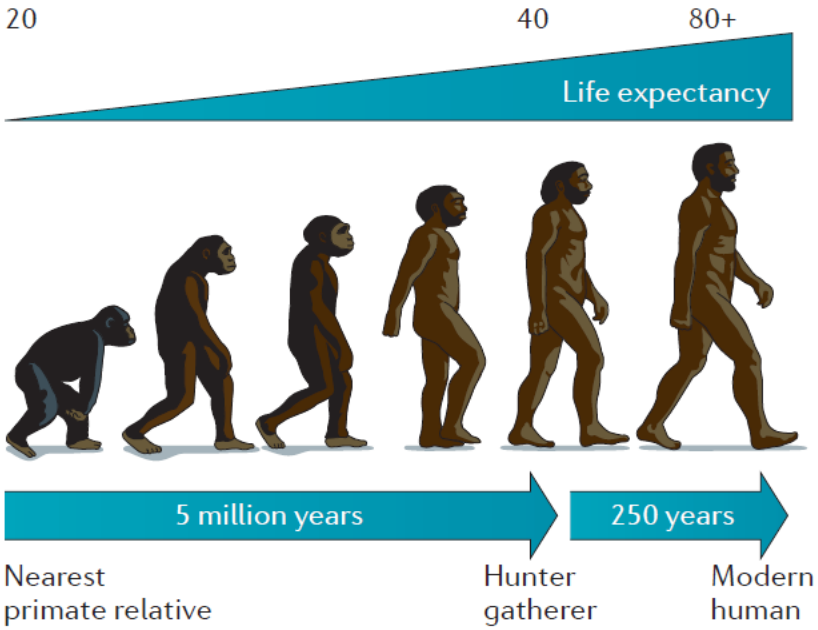


Figure 2

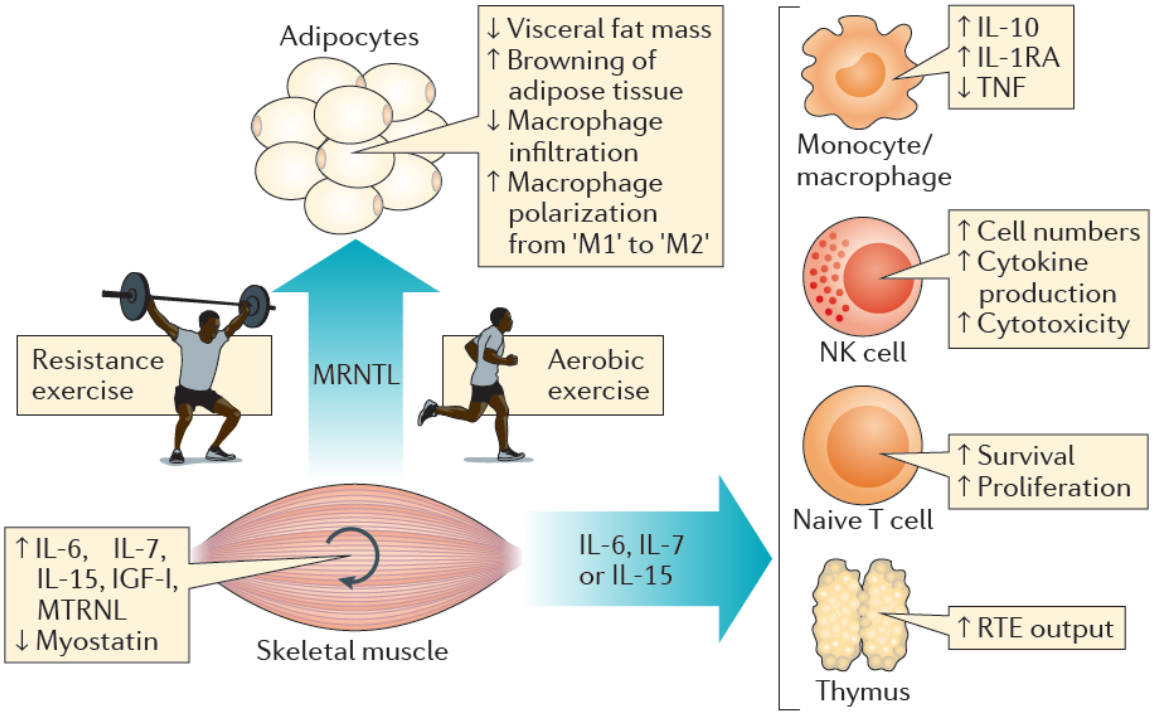
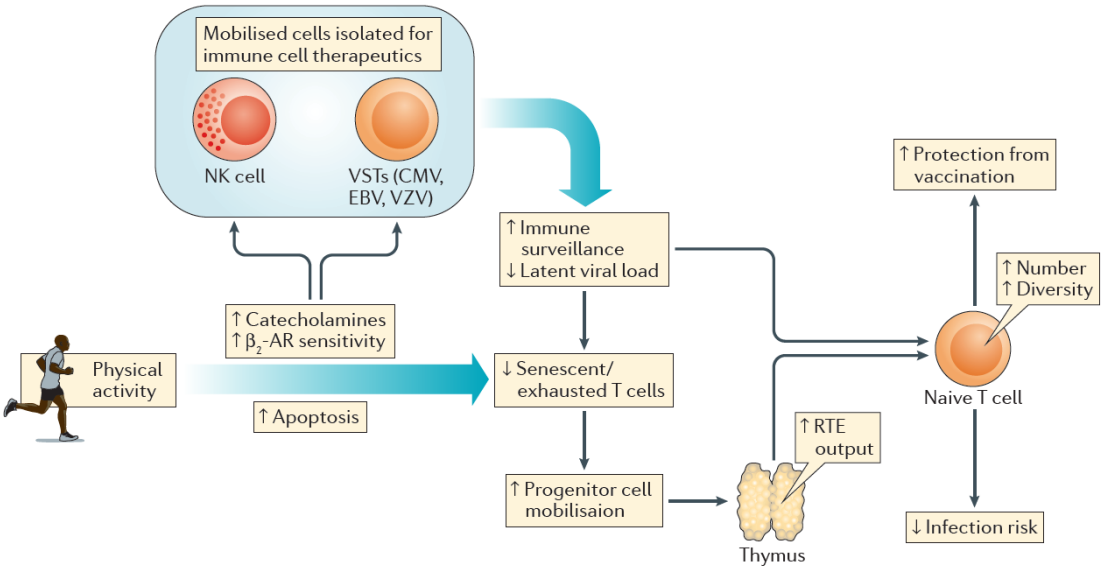


Figure 3


Mobilised cells isolated for immune cell therapeutics
NK cell
VSTs (CMV, EBV, VZV)
↑ Immune surveillance
↓ Latent viral load
↑ Protection from vaccination
↑ Number
↑ Diversity
↑ Catecholamines
↑ β_2-AR sensitivity
Physical activity
↑ Apoptosis
↓ Senescent/ exhausted T cells
Naive T cell
↑ RTE output
↑ Progenitor cell mobilisaion
Thymus
↓ Infection risk